BLOOD-BRAIN BARRIER TRANSMIGRATING COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that transmigrate the blood-brain barrier, and uses thereof. More specifically, the present invention relates to compounds that may comprise an antibody or fragment thereof that crosses the blood-brain barrier, an immunoglobulin Fc domain or fragment thereof, and a polypeptide binding to beta-amyloid, fusion proteins and compositions thereof and their use in the treatment of Alzheimer's disease.

BACKGROUND OF THE INVENTION

[0002] Neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, are an increasing burden on our ageing society because there are currently no effective treatments for these disabling conditions. Alzheimer's disease (AD) is an irreversible neurodegenerative disorder affecting approximately 15% of the population over 65 years of age and is the predominant cause of progressive intellectual and cognitive failure in the ageing population (Hardy et al, 2014).

[0003] In AD, there is a severe loss of cholinergic neurons with a consequent decline in the levels of acetylcholine (ACh), a key neurotransmitter involved in memory processing and storage. In addition, excitotoxicity induced by neurotransmitter glutamate is also implicated in the pathogenesis of AD. Therefore, cholinergic augmentation and/or inhibition of glutamate toxicity might improve cognition in AD. Indeed, the only FDA approved drugs for the treatment of AD are acetylcholine esterase (AChE) inhibitors (e.g., donepezil, rivastigmine, galantamine) to prevent the loss of ACh and inhibitors of specific glutamate receptors (e.g., memantine) (Mangialasche et al, 2010; Ji and Ha, 2010; Savonenko et al, 2012). However, the beneficial effects of these symptomatic drugs are limited and transient, providing temporary improvement in cognitive functions and do not stop the progression of the disease. While other treatments including antioxidants, anti-inflammatory drugs (NSAIDS), cholesterol-lowering drugs and estrogen therapy are considered, none of these treatments appear to have any long-term beneficial effects, particularly in improving memory and cognitive function in AD patients (Magialasche et al, 2010; Ji and Ha, 2010).

[0004] A major hallmark of Alzheimer's disease is the accumulation of a 39-43 amino acid peptide β-amyloid (Aβ) in the brain in the form of aggregates and plaques. A considerable body of evidence based on genetic, pathological and biochemical studies indicate that Aβ, particularly its oligomeric aggregates, plays a central role in the development of AD pathology (Hardy et al, 2014; DeLaGarza, 2003; Selkoe and Hardy, 2016). According to amyloid hypothesis, a chronic imbalance in the production and clearance of Aβ in the brain results in its accumulation and aggregation with ageing. These Aβ aggregates are believed to initiate a cascade of events leading to synaptic loss and neuronal functions, leading to a progressive loss of memory and other cognitive functions (Hardy et al, 2014; DeLaGarza, 2003; Selkoe and Hardy, 2016; Sengupta et al, 2016).

[0005] The generation of Aβ from its precursor protein APP is achieved by the sequential proteolysis of APP by proteases β, and γ secretases (Barageb and Sonawane, 2015). Inhibitors of these enzymes have been shown to reduce Aβ production and are being developed as potential drugs for treating AD (Hardy et al, 2014; Mangialasche et al, 2010; Selkoe and Hardy, 2016; Ji and Ha, 2010). Similarly, agents that sequester and/or promote Aβ clearance are also being developed. Notable among these are the development of immunotherapies with AD vaccine. Both active (Aβ peptides) and passive immunization (Aß-antibodies) have been shown to be effective in preventing amyloid deposition as well as clearing of preformed amyloid plaques in transgenic animal models of AD and in clinical trials involving AD patients (Mangialasche et al, 2010; Ji and Ha, 2010; Morrone et al, 2015; Lannfelt et al, 2014; Selkoe and Hardy, 2016; Goure et al, 2014).

[0006] Inhibitors of β and γ secretases that prevent proteolytic cleavage of amyloid precursor protein (APP) and thereby reduce or suppress brain Aβ production are being developed (e.g., tarenflurbil, semagacestat, verubecestat). However, their therapeutic efficacy in reducing Aβ burden is not yet known and many of these drugs have failed in pre-clinical or clinical trials (Savonenko et al, 2012; Musiek and Holtzman, 2015). Moreover, since these enzymes are also involved in the processing of other enzymes and signaling molecules such as Notch that are linked to neuronal development (Savonenko et al, 2012; Musiek and Holtzman, 2015), these inhibitors may have serious non-specific side effects.

[0007] Immunotherapeutic approaches such as active (Aß vaccine, AN1792) and passive immunization (e.g., Bapineuzumab, Solanezumab, Crenezumab, aducanumab etc) have been shown to be quite effective in reducing Aβ deposition and partial elimination of memory deficits in transgenic animals (Monsonego and Weiner, 2003; Bard et al, 2000, Sevigny J et al., 2016). Several clinical trials using both active and passive immunization have shown reduction in brain Aβ deposition with moderate improvement in cognition. However, clinical trials had to be abandoned due to severe inflammatory reactions (meningo-encephalitic presentation), vasogenic edema, and micro-haemorrhages in AD patients. Despite these limitations, the immunotherapy approach indicates that agents that effectively sequester Aβ, and prevent its deposition and toxicity, could potentially serve as effective drugs in arresting the progression of AD, and even prevent its development (Rafii and Aisen, 2015, Selkoe and Hardy, 2016).

[0008] Treatment as well as early diagnosis of AD and other diseases that originate in the brain remain challenging because the majority of suitable therapeutic molecules and diagnostics cannot penetrate the tight and highly restrictive blood-brain barrier (BBB) (Abbott, 2013). The BBB constitutes a physical barricade that is formed by brain endothelial cells (BECs) that line the blood vessels and connect with each other through tight junctions (Abbott, 2013). The tight junctions formed between the BECs are essential for the integrity of the BBB and prevent the paracellular transport of molecules larger than 500 daltons (Da). Because brain endothelial cells exhibit very low pinocytosis rates (Abbott, 2013), transcellular transport of larger molecules is limited to the highly specific receptor mediated transcytosis (RMT) pathway, and the passive, charge-based adsorption mediated transcytosis (Abbott, 2013; Pardridge, 2002). Additionally, the high density of efflux pumps, such as P-glycoprotein or